the amount of repair. In addition, it established that repair was initiated only during exposure because if initiation of repair were a continuing process, the observed correlation between exposure time and repair should not have existed.

These data demonstrate that the greater biological effects obtained with simultaneous dual exposures were an exposure rate effect rather than a result of increased homogeneity. Therefore, the prerequisite for increasing the biological effectiveness of uniform radiation was an increase in the exposure rate.

Although it has been customary to convert roentgens as calibrations in air to calculated absorbed doses at the midline, expressed in rad or Grays, it was obvious that conversion was not applicable for total-body exposure when hematopoietic cells were the target, since distribution of target tissue significantly altered both the severity of the cellular damage and repair capabilities of damaged cells in these small animals. This conversion would have ignored the greater effectiveness of the homogeneous dual exposure compared with the uniform dorsal and nonuniform ventral exposures as a function of the target organs and their spatial relationship to the radiation source. These factors would undoubtedly increase in importance when larger animals receive total-body exposures.

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Are Cell Number and Cell Proliferation Risk Factors for Cancer?[1]

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Relatively little is known about the mechanisms underlying carcinogenesis in humans. Caloric restriction strongly inhibits the development of neoplasia in rodents, and there is evidence of a positive relationship between cancer and body weight in humans. Caloric restriction early in life is also known to permanently diminish organ cellularity. A recent link between adult stature and cancer incidence similarly implicates a lasting effect for growth and possibly for early nutrition in carcinogenesis. It is postulated that cancer risk is proportional to the number of proliferating cells, which in turn depends on both the number of cells and the rate of cell division within the tissue. This hypothesis is consistent with several aspects of human carcinogenesis, including multistage models and the epithelial origin of most cancers. [J Natl Cancer Inst 1988;80:772-775]

Although a large number of factors have been associated with the development of malignant neoplasms in humans, the mechanisms involved are still largely unknown. The multistage models of carcinogenesis, particularly the initiation-promotion scheme, which has been demonstrated primarily in animal models, have received the greatest attention in this regard and serve as a cornerstone of current hypotheses on biological mechanisms (*1-4*). One of the most outstanding features of cancer, its exponential increase with age in humans as well as in most other species, has been explained in terms of an accumulation of deleterious genomic events in somatic cells (*1,2,5,6*). According to this "somatic mutation" model, a critical number or combination (or both) of heritable alterations must occur in order that a malignant transformation take place in, presumably, one cell. Two factors implicit in, and of critical importance to, these theories are, first, the number of cells available and, therefore, at risk for transformation, and second, the rate of cell division (i.e., mitosis).

Caloric restriction, a potent dietary modification, is known to affect cell number, cell proliferation, and carcinogenesis in rodents (*7-9*). Earlier observations in this area, combined with recent developments in the study of body size-cancer relationships, may substantiate the critical role played by cell number and proliferation in the above theories and offer new insight into the mechanisms involved in carcinogenesis.

Caloric Restriction and Carcinogenesis

Restricting the calorie intake of rodents inhibits the development of a variety of tumors, both "spontaneous" and chemically induced, including carcinomas and sarcomas (*9-11*). Incidence is either completely prevented or decreased and delayed to later ages in comparison to that in animals fed ad libitum. Life span is lengthened and the development of other pathology is also reduced by limiting energy intake. While restriction beginning early in life (e.g., at weaning) appears to be the most efficacious intervention, later modification shows similar effects (*10,12,13*). In this respect, although stunting growth is not a prerequisite to tumor inhibition, body weight reduction (including both lean and fat tissue) is involved (*9,11,14*). The observation that calorie restriction after exposure to a "one-step" chemical carcinogen is more effective than calorie reduction before (or during) such exposure suggests that calorie restriction has antipromotional (i.e., late-stage) properties.

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Data on energy balance in humans are sparser and have been reviewed recently (*15*). In all, they provide evidence for a positive relationship between energy intake or relative body weight and cancer, notably for cancer of the breast (*16-18*), colorectum (*18-20*), prostate (*18,21*), and endometrium (*18,22*).

Adult Stature and Cancer

In a recent report, short individuals (particularly men) demonstrated roughly two-thirds the cancer rate of taller persons, with several other risk factors, including fatness, taken into account (*23*). The association was strongest for cancer of the large bowel and breast. Tallness has been related to elevated risk of several specific cancers, including breast, lung, acute lymphocytic leukemia, Hodgkin's disease, and osteogenic sarcoma (*16,17,24-27*). Adult stature is not only genetically determined but can be influenced by environmental events early in life. Early caloric restriction results in permanent growth stunting and reduced stature and therefore is one determinant of adult stature. Some short individuals could therefore have experienced macronutrient restriction during growth that was sufficient to diminish both their ultimate stature and their risk of cancer (*23,28*), while others are genetically short.

Effects of Caloric Restriction: Possible Mechanisms

Caloric restriction has been shown to alter a wide range of physiologic functions, including body temperature, basal metabolic rate, protein synthesis and enzyme activity levels, cell-mediated immunity, and endocrine status (i.e., levels of pituitary hormones, insulin, T_3 and T_4, and 17-ketosteroids) (*29-34*). Theories about the relevance of the various effects of caloric restriction to carcinogenesis have focused on the endocrine and immune systems (*34-36*) and mitotic activity (*8*). An essential role for most of these factors in human carcinogenesis has yet to be established, however.

Cell division, an energy-dependent process, decreases during caloric restriction (*8*). Caloric restriction early in development also leads to reduced hyperplastic growth of most (if not all) organs and, consequently, a lower total number of cells (*7*). By contrast, later restriction results in a decrease in cell size with very little effect on cell number; the former change in permanent, whereas the latter is reversible when food intake is increased (*7*). Thus, any animal that is undernourished during the hyperplastic growth period has a reduced number of cells in all organs studied to date. Although most organs, including brain, lung, liver, heart, kidney, and skeletal muscle, have been investigated, colon (particularly colonic mucosa) and breast ductile tissue have not. One of these regenerating tissues, the colon, has been examined, however, in undernourished adult animals and displays a reduced rate of cell division (*37*). The effects of caloric restriction therefore depend on the timing of the restriction. Early restriction will permanently stunt growth and reduce total cell number in all organs. Later restriction will reduce body fatness, cell size, and the rate of cell turnover in regenerating tissues.

Hypothesized Role for Cell Number and Proliferation

It is proposed that, within any one species, cancer risk is proportional to both cell number and the rate of cell division. Carcinogenesis can be increased by either increasing the number of cells at risk for exposure to the relevant transforming factors or increasing the mitotic activity of a tissue. The latter event could serve to propagate a transformation or cause cellular DNA to be made vulnerable (e.g., during DNA replication) to carcinogenic factors. This idea is supported by observations showing that tumor incidence increases when carcinogen exposure takes place during periods of rapid cell division (*38,39*) and decreases when DNA synthesis is inhibited by dactinomycin (*40*). Alternatively, shorter cell cycles may lessen the degree of DNA repair occurring prior to the next division, thereby permitting greater inheritance of genomic efforts. Given an equivalent rate of cell proliferation, a larger organ of greater cellularity [e.g., the colonic mucosa in very tall individuals (*41*)] is more likely to have one of its cells undergo malignant transformation. This was indeed the case in the prospective study cited above, which demonstrated that the tallest persons have twice the rate of colorectal cancer of the shortest individuals (*23*). Conversely, in persons of similar stature, organ size, and cellularity, those with higher rates of cell division are at greater risk.

This conceptualization of cumulative cell division is consistent with both the age-incidence pattern of adult cancers and multistage models of carcinogenesis. The effectiveness of increased cell proliferation in promoting carcinogenesis could, in part, contribute to the role of diverse causative factors, such as tobacco smoke, ethanol, aflatoxin, and UV or gamma irradiation, all of which are capable of either stimulating cell division locally (*42-45*) or expressing their carcinogenic potential following mitosis (*46*). The hypothesis accounts for the fact that the majority of human malignancies originate in epithelial organs, since it is largely in these tissues that stem cell division continues throughout life in order to replenish used and lost cells. One revealing exception concerns long bone epiphyses, which are prone to the development of osteogenic sarcoma during the adolescent growth spurt, particularly among taller individuals (*27*). That relatively few adult malignancies result from hematopoietic elements (i.e., a nonepithelial yet highly proliferative tissue) may be accounted for by the high level of cell amplification that occurs during hematopoiesis, which most likely results in fewer life-time stem cell divisions than in, for example, colonic epithelium. The etiologic significance of predisposing conditions such as breast intraductal and endometrial adenomatous hyperplasia, polyposis coli, and hyperplastic nodules of the liver, which involve abnormally high levels of cellular proliferation, can also be explained.

Both components of this hypothesis are relevant clinically. Individuals who are both tall and overweight would be predicted to experience higher rates of carcinoma. Recent analysis of a very large U.S. cohort demonstrates this trend, particularly for cancer of the

breast and colorectum (Garfinkel L, Albanes D: unpublished observations). Weight reduction and enhanced early detection efforts are warranted in this subgroup of individuals. Of additional interest is the potential for developing early screening tests based on the level of cell proliferation. Work in this area has focused on the colon (*47*) [and, most recently, esophagus (*48*)] in humans and in rodents (*37*), although animal experiments have also explored other sites; for example, rates of DNA synthesis as predictors of mammary carcinoma (*49*). Measures that have the potential to slow the rate of cell division (e.g., reducing body weight or energy intake relative to requirements) may lower the risk not only of cancer, but also of other chronic diseases, and overall mortality as well. Indeed, since caloric restriction has been known for some time to increase longevity (*13,50*), it is conceivable that the mechanism for this effect involves slowed stem cell turnover, with a concomitant reduction in DNA utilization. This concept of caloric restriction and aging is supported by the fact that the number of cell generations is limited in vitro (*51*).

Conclusions

While cell replacement is essential to human life, excessive proliferation and large body and organ size are not. The present hypothesis explains how caloric restriction inhibits carcinogenesis and why taller individuals experience higher rates of cancer. It also suggests ways to modify or reduce the development of cancer. Research is needed to test this hypothesis and identify specific markers of abnormal (i.e., preneoplastic) cell proliferation.

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